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# Stereoelectronic and dynamical effects dictate nitrogen inversion during valence isomerism in benzene imine†

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Benzene imine (**1**)  $\rightleftharpoons$  1*H*-azepine (**2**) isomerization occurs through sequential valence and *endo*-*exo* isomerism. Quantum chemical and quasiclassical trajectory (QCT) simulations reveal the coupled reaction pathway – ring-expansion followed by N-inversion to the most stable isomer, *exo*-1*H*-azepine (**Exo-2**). Direct-dynamics produce a mixture of *endo*- and *exo*-1*H*-azepine stereoisomers and govern the *endo*-1*H*-azepine (**Endo-2**)  $\rightleftharpoons$  *exo*-1*H*-azepine (**Exo-2**) ratio. **Exo-2** is computationally identified as the most stable product while **Endo-2** is fleetingly stable with a survival time ( $S_T$ )  $\sim$ 50 fs. *N*-Methyl substitution exclusively results in an *exo*-1-methyl-1*H*-azepine isomer. F-substitution at the N-site increases the barrier for N-inversion and alters the preference by stabilizing **Endo-2**. Interestingly, the *exo*-1-fluoro-1*H*-azepine (minor product) is formed through bifurcation *via* non-statistical dynamics. A highly concaved Arrhenius plot for **1a**  $\rightarrow$  **2a** highlights the influence of heavy-atom tunneling on valence isomerism, particularly at low temperatures. Heavy-atom tunneling also results in a normal N–H(D) secondary KIE above 100 K even though the increase in hybridization from  $sp^2$  to  $sp^3$  at nitrogen should cause an inverse KIE classically.

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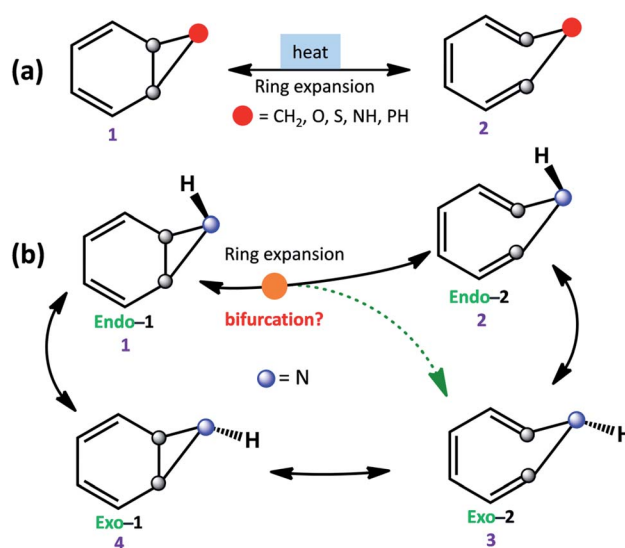
## Introduction

The equilibrium between bicyclo[4.1.0]hepta-2,4-diene and cyclo-hepta-1,3,5-triene has been a subject of active interest.<sup>1</sup> Ring-expansion is also known for oxygen (benzene-oxide  $\rightleftharpoons$  oxepin), nitrogen (benzene imine  $\rightleftharpoons$  1*H*-azepine), sulfur (benzene sulfide  $\rightleftharpoons$  thiepine), and phosphorus (benzene phosphane  $\rightleftharpoons$  1*H*-phosphepine).<sup>2,3</sup> All of them undergo disrotatory electrocyclic rearrangement to form the ring-opened product.<sup>4</sup> However, stereoelectronic induction can influence the reaction mechanism and conformations of strained molecules (see Scheme 1a).<sup>5,6</sup>

For example, 1*H*-azepine with  $8\pi$ -electrons exists in a boat conformation as expected from its anti-aromatic Hückel electron count.<sup>7</sup> Based on DFT calculations, Dardonville *et al.* estimated an anti-aromatic destabilization of 10.8 kcal mol<sup>-1</sup> for 1*H*-azepine by computing its protonation energies.<sup>8</sup> Ragyanszki and co-workers studied the oxidation of the anti-aromatic *N*-methyl-1*H*-azepine to the non-aromatic *N*-oxide of azepine.<sup>9</sup> 1*H*-

Azepine, and its derivatives are also known to undergo rapid dimerization *via*  $(6 + 4)\pi$  *exo*-cycloaddition.<sup>10</sup>

Further, ring expansion of benzene imine into 1*H*-azepine (**1**  $\rightarrow$  **2**) can in-principle also be accompanied by an inversion at the N-center (see Scheme 1b). Since the NMR spectra of 1*H*-

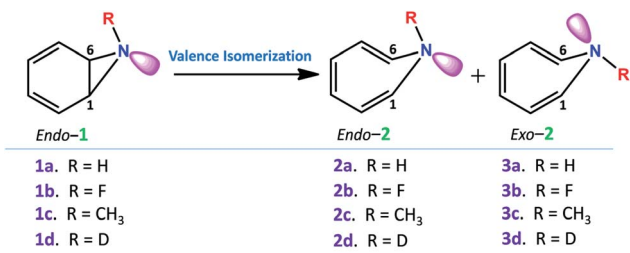


**Scheme 1** (a) Ring expansion reactions in substituted bicyclo[4.1.0]hepta-2,4-dienes. (b) Schematic possible reaction pathways for benzene imine (**1**).

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† Electronic supplementary information (ESI) available: Schematic potential energy surfaces, QCT inputs, details of MD simulations, QMT inputs, CVT and CVT + SCT rates for valence isomerism, NBO analyses, Cartesian coordinates, energies, and harmonic frequencies and Awk Code. See DOI: 10.1039/d1sc04855d





Scheme 2 Valence isomerism in benzene imine (1) derivatives to their 1H-azepine (2) analogs.

azepine remain invariant in the range  $-90\text{ }^{\circ}\text{C}$  to  $+130\text{ }^{\circ}\text{C}$ , Paquette *et al.* suggested that the inversion barrier should be less than  $5.7\text{ kcal mol}^{-1}$ .<sup>11</sup> Additionally, they could not gather any signature for the existence of benzene imine in this temperature range. Therefore, **Exo-2** is expected to be the thermodynamically most stable product. However, the mechanism is still unknown and a possible reaction pathway can be either stepwise ( $1 \rightarrow 2 \rightarrow 3$ ) or coupled ( $1 \rightarrow 2, 3$ ) for the formation of 1H-azepine analogs.

In Scheme 2, we have used different substitutions at the N-site to examine the stereoelectronic effects on the valence isomerization of **Endo-1**. Obtaining a detailed reaction mechanism and understanding the effect of the stereoelectronic influence on the potential energy surface for the **Endo-1**  $\rightarrow$  **Endo-2/Exo-2** isomerizations require further time-resolved mechanistic investigation using quasi-classical MD simulations.<sup>12–14</sup> Additionally, the dynamics at sub-cryogenic temperatures would be dictated by quantum mechanical tunneling (QMT) instead of over-the-barrier crossing at ambient temperatures.<sup>15–27</sup> In this context recently, Sander and co-workers have reported unequivocal signatures of heavy-atom tunneling for the benzene oxide – oxepin equilibrium at 3 K.<sup>28</sup> The present article investigates post-transition state bifurcation reaction pathways for benzene imine  $\rightleftharpoons$  1H-azepine. MD simulations were performed from the rate-limiting transition states to decipher the non-statistical effects on the stereoselectivity (**Endo-2** : **Exo-2**) during the valence isomerism.<sup>29</sup> Heavy-atom tunneling is shown to be the major pathway for ring expansion, particularly at low temperatures.

## Computational details

Geometry optimization was performed at the M06-2X/6-31+G(d,p) level of theory with the Gaussian 16 (ver A.03) suite of programs (see the ESI, Page S2† for calibration and benchmarking).<sup>30,31</sup> Reaction energies and activation barriers were investigated for **Endo-1**  $\rightarrow$  **Exo-1**, **Endo-2**, **Exo-2**, and their analogs (R =  $-F$ , and  $-CH_3$ ). The reactant, product, and transition-state were confirmed by intrinsic reaction coordinate (IRC) and harmonic frequency calculations.<sup>32</sup> In addition, for computation of the reaction rates at low temperatures, the transition states (TS) were located using canonical variational transition-state theory (CVT) along the reaction paths where free-energy maximizes at the same level as used for geometry

minimization.<sup>33</sup> Tunneling corrections were incorporated within the rate coefficient calculations using the small-curvature tunneling (SCT) approximation.<sup>34</sup> These were implemented within Gaussrate 17-B by interfacing with Gaussian 16 and Polyrate 17-C.<sup>35,36</sup> Quantized reactant state tunneling (QRST) calculations were performed to determine the reaction rates accurately at sub-cryogenic temperatures.<sup>37</sup>

Further, the ambient temperature behavior of **Endo-1** for R =  $-H$ ,  $-F$ , and  $-CH_3$  was studied using quasiclassical direct-dynamics simulations in the gas phase at 298.15 K. Reaction trajectories were simulated from rate-limiting sampled **TS(1**  $\rightarrow$  **2)** structures using the Singleton's Progdyn code interfaced with Gaussian 16 (see the ESI for TS-sampling details, Fig. S4†).<sup>38–41</sup> The reaction trajectories were simulated to the forward and backward directions until either one of the products or the reactants is formed. The classical equations of motion were integrated with a velocity-Verlet algorithm.<sup>42</sup> The energies and derivatives were calculated on the fly with the M06-2X/6-31+G(d,p) level. The time step for integration is 1 fs. Thresholds for bond formations, trajectory terminations, and in-house code for trajectory characterization are shown on Page S8 and S50.†

## Results and discussion

Benzene imine (**Endo-1**) can isomerize to *exo*-1H-azepine (**Exo-2**) either by ring expansion followed by N-inversion or *vice versa*. Both the plausible pathways are presented in Fig. 1.

Each involves two steps and crossing two barriers, namely  $1 \rightarrow 2 \rightarrow 3$  or  $1 \rightarrow 4 \rightarrow 3$  with  $\Delta G_{1 \rightarrow 2}^{\ddagger}$  followed by  $\Delta G_{2 \rightarrow 3}^{\ddagger}$  or  $\Delta G_{1 \rightarrow 4}^{\ddagger}$  followed by  $\Delta G_{4 \rightarrow 3}^{\ddagger}$  respectively. The kinetic preference

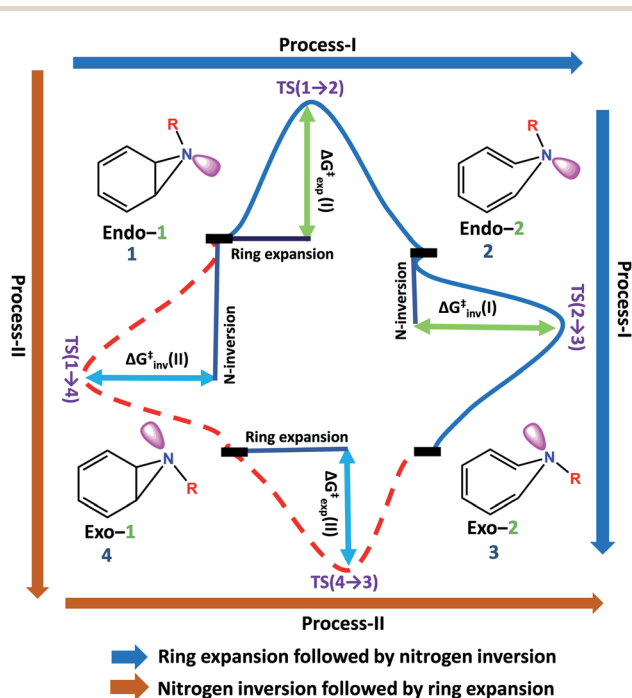


Fig. 1 Two plausible mechanistic pathways for the formation of *exo*-1H-azepine, **Exo-2** from benzene imine, **Endo-1**.



**Table 1** Relative free energies and free energies of activation at 298.15 K (in kcal mol<sup>-1</sup>) for 1 → 2 → 3 and 1 → 4 → 3 at the M06-2X/6-31+G(d,p) level of theory

	1a (R = H)	1b (R = F)	1c (R = CH <sub>3</sub> )
1 ( <b>Endo-1</b> )	0.0	0.0	0.0
$\Delta G_{1 \rightarrow 2}^\ddagger$	4.4	5.7	5.2
2 ( <b>Endo-2</b> )	0.3	-0.1	0.6
$\Delta G_{2 \rightarrow 3}^\ddagger$	1.4	6.7	0.5
3 ( <b>Exo-2</b> )	-2.7	-2.0	-3.8
$\Delta G_{1 \rightarrow 4}^\ddagger$	18.0	—	17.1
4 ( <b>Exo-1</b> )	3.7	-0.5	1.4
$\Delta G_{4 \rightarrow 3}^\ddagger$	5.5	6.4	4.3

of either depends on the relative magnitudes of these barriers. Table 1 lists them for the various substituents on the nitrogen head. The *exo-1H*-azepine **Exo-2** is the most stable isomer irrespective of the substituent. Therefore, the benzene imine ⇌ *1H*-azepine equilibrium will shift towards the *1H*-azepine side. This result is in agreement with previous experiments.<sup>11</sup>

In terms of the preference for either 1 → 2 → 3 or 1 → 4 → 3 (see Fig. 1), ring expansion followed by the inversion pathway (a process-I) is more favorable than inversion followed by expansion (process-II). For example, in **1a**,  $\Delta G_{1 \rightarrow 2}^\ddagger = 4.4$  kcal mol<sup>-1</sup> and  $\Delta G_{2 \rightarrow 3}^\ddagger = 1.4$  kcal mol<sup>-1</sup> while  $\Delta G_{1 \rightarrow 4}^\ddagger = 18.0$  kcal mol<sup>-1</sup> and  $\Delta G_{4 \rightarrow 3}^\ddagger = 5.5$  kcal mol<sup>-1</sup>.

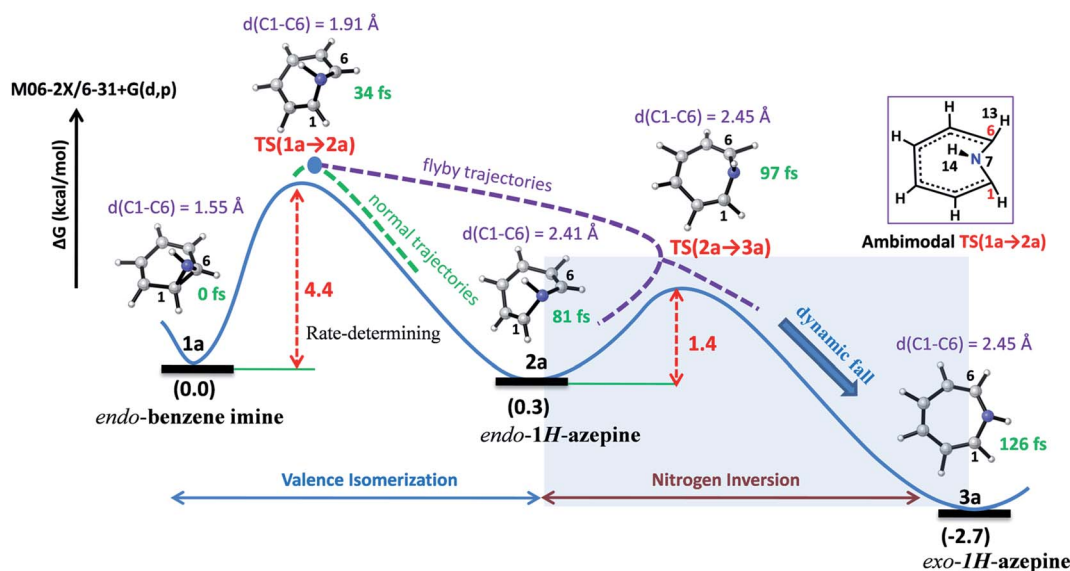
The high inversion barrier for **Endo-1** → **Exo-1** ( $\Delta G_{1 \rightarrow 4}^\ddagger$  (inversion) = 18.0 and 17.1 kcal mol<sup>-1</sup> for **1a** and **1c** respectively) arises due to the ring-strain in the three-membered azaring, which aggravates in the transition-state due to the planarity of the N-site. In contrast, the stereoelectronic modulation using R = -F leads to the cleavage of the bridging bond (rate-limiting step) of the **1b** and disfavors the planarity of N-F with the cyclopropane ring in **TS(1 → 4)** for the 1 → 4 → 3 reaction pathway and therefore, its TS could not be located (process-II).<sup>43</sup>

Following the kinetically favorable 1 → 2 → 3 pathway (coupled valence isomerism along the C-C bond and *endo-exo* isomerism *via* N-inversion) **1a**, **1b**, and **1c** show remarkable variation in their relative  $\Delta G_{1 \rightarrow 2}^\ddagger$  (expansion) and  $\Delta G_{2 \rightarrow 3}^\ddagger$  (inversion). For **1a** the free-energy of activation for ring expansion is three times more than that for inversion, while for **1b**, both the barriers are comparable. For **1c**, the activation barrier for N-inversion is the smallest,  $\Delta G_{2c \rightarrow 3c}^\ddagger = 0.5$  kcal mol<sup>-1</sup>. Ironically, **1b** and **1c** are isoelectronic, yet their significant differences in the N-inversion barriers make them ideal candidates to compare the product distributions between *endo*- and *exo-1H*-azepine conformational isomers *viz.* **2b/3b** and **2c/3c** and contrast with the parent benzene imine ⇌ *1H*-azepine, **2a/3a**. See ESI Fig. S1–S3† for schematic potential energy surfaces for **1a**, **1b**, and **1c**.

Valence isomerism in *endo*-benzene imine is an example of a dynamically rich system where rapid C-C bond dissociation assists N-H inversion. The rate-limiting C1-C6 bond activation facilitates both the ring expansion and N-inversion (see Fig. 2). The quasiclassical direct-MD simulations reveal a chameleonic transition state **TS(1a → 2a)** and the non-statistical effects on the product count (**Endo-2** : **Exo-2**).<sup>44–48</sup>

Fig. 2 depicts a typical trajectory and the time-resolved formation of azepine isomers (**2a** and **3a**). A total of 142 reaction trajectories were propagated from rate-limiting **TS(1a → 2a)** (see ESI Fig. S4† for details). The reaction trajectories passing through the **TS(1a → 2a)** zone can be characterized as “normal” trajectories if they follow the IRC-pathway (1 → 2 → 3) or “flyby” trajectories when they skip the minimum energy pathway (bypassing the **2a**-zone) and directly traverse to **TS(2a → 3a)**, finally forming **3a**.

Out of the 142 reaction trajectories, 108 (76%) “normal” reaction trajectories led to *exo-1H*-azepine (**3a**) while 20 (14%) “flyby” reaction trajectories afford the **TS(2a → 3a)** and finally fall to the *exo-1H*-azepine (**3a**) zone. Only 6 (4%) trajectories are



**Fig. 2** Representative reaction pathways for the valence isomerization assisted nitrogen inversion of **1a**.



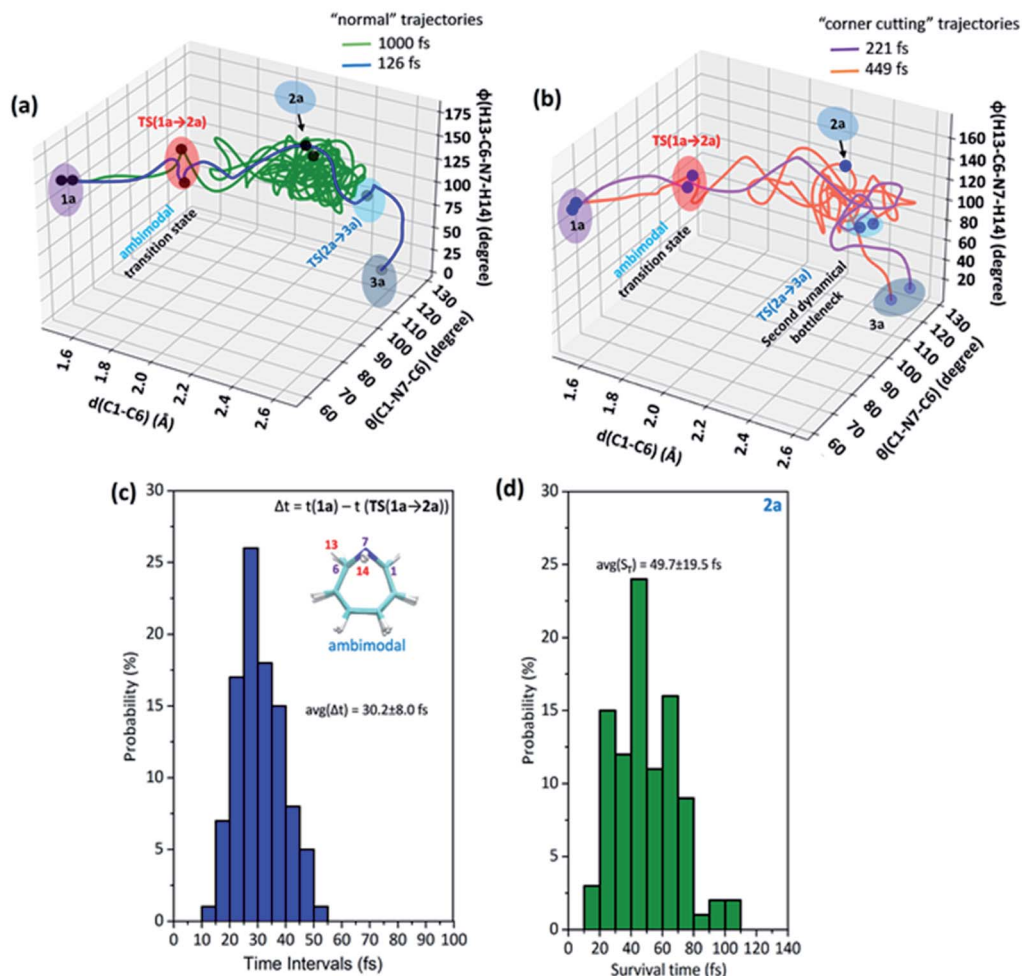


Fig. 3 (a) "Normal" trajectories represent the pathways for the formation of **2a** and **3a**, (b) "flyby" trajectories traverse to  $\text{TS}(2a \rightarrow 3a)$  and eventually fall to the **3a** product side, the (c) average time ( $\Delta t$ ) required for the  $1a \rightarrow \text{TS}(1a \rightarrow 2a)$  path and the (d) average survival time ( $S_T$ ) for the endo-1H-azepine (**2a**) product.

found in the simulation that produces endo-1H-azepine (**2a**) up to 1 ps. The remaining 8 (6%) re-cross to either the reactant (**1a**) or product (**3a**) zones. This indicates a post-transition state bifurcation reaction where dynamical effects govern the stereoselectivity. The selectivity (**2a** : **3a**) for the  $1a \rightarrow 2a, 3a$  ring-opening reaction is  $\sim 1 : 21$ .

Further, Fig. 3(a) represents two "normal" reaction trajectory propagations and time-resolved variation of the critical structural parameters ( $d$ ,  $\theta$ , and  $\phi$ ) during valence isomerization (benzene imine  $\rightarrow$  1H-azepine). The green-colored trajectory defines the reaction path that affords endo-1H-azepine (**2a**) which is found stable up to 1 ps during MD simulation. In contrast, the blue trajectory follows the ultrafast decay along the steepest descent path and eventually falls towards the exo-1H-azepine (**3a**) product zone.

These flyby reaction trajectories were found highly concerted and follow shorter dynamical routes to reach the **3a**-product zone in the potential energy surface. In Fig. 3(b) a typical "flyby" trajectory (violet line) shows its transit from  $\text{TS}(1a \rightarrow 2a)$  to  $\text{TS}(2a \rightarrow 3a)$  and falls into the **3a**-product basin without

forming Endo-2 (**2a**). On the other hand, the orange line first approaches the  $\text{TS}(2a \rightarrow 3a)$  zone, takes a short trip at the **2a**-zone, and finally populates the exo-1H-azepine, Exo-2 (**3a**) basin.<sup>49</sup>

Further, the lower thermodynamic stability of endo-1H-azepine ( $\Delta G$  (**2a** and **3a**) = 3.0 kcal mol<sup>-1</sup>) and small activation barrier ( $\Delta G^\ddagger = 1.4$  kcal mol<sup>-1</sup>) for the N-H inversion populates the **3a** product basin. From Fig. 3(c), we can estimate that the average time ( $\Delta t$ ) required to reach the rate-limiting transition state  $\text{TS}(1a \rightarrow 2a)$  is  $30.2 \pm 8.0$  fs. We have also calculated the survival time ( $S_T$ ) using the cut-offs: **2a** appears when  $d(\text{C1-C6}) > 2.19$  Å,  $\theta(\text{C1-N7-C6}) > 98^\circ$  and  $\phi(\text{H13-C6-N7-H14}) > 135^\circ$  whereas **2a** disappears when  $d(\text{C1-C6}) > 2.38$  Å,  $\theta(\text{C1-N7-C6}) > 98^\circ$  and  $\phi(\text{H13-C6-N7-H14}) > 104^\circ$ . The survival time ( $S_T$ ) vs. probability plot indicates that the average survival time ( $S_T$ ) of **2a** is  $49.7 \pm 19.5$  fs (see Fig. 3(d)). Therefore, the signature of the endo-1H-azepine (**2a**) formation can be traced using spectroscopic techniques.<sup>50,51</sup>

Additionally, the electronic and dynamical effect control on stereoselectivity was investigated by introducing R = -F and



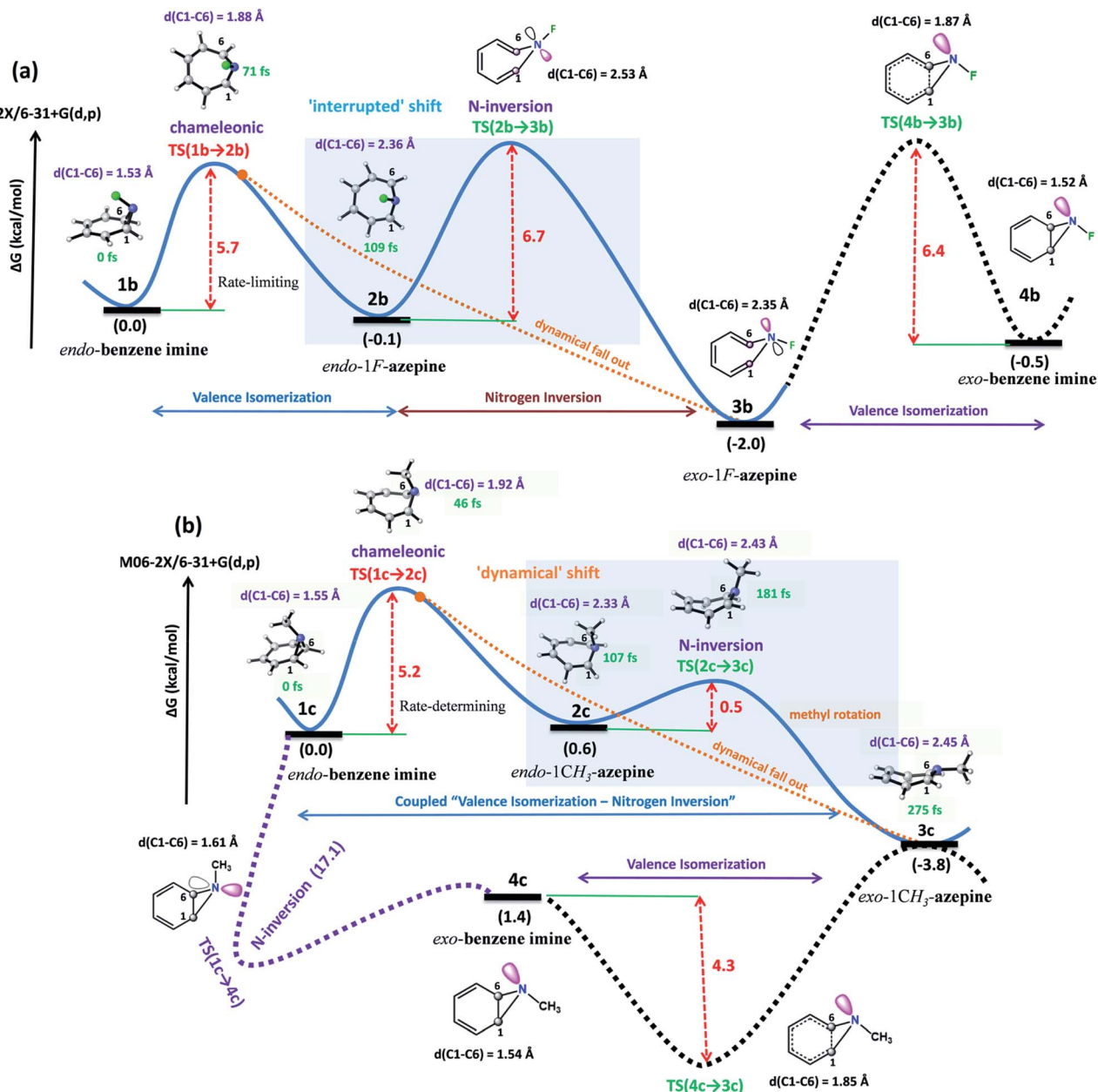


Fig. 4 (a and b) Evolution of the potential energy surfaces, where “interrupted” shift and “dynamical” shift denote the modification strategies to isolate the *endo*-1*F*-azepine (**2b**) and *exo*-1*CH*<sub>3</sub>-azepine (**3c**), respectively.

-CH<sub>3</sub> at the inversion center. In Fig. 4(a), the relative free energy surface dictates an “interrupted” shift.<sup>52</sup> The valence isomerism mediated inversion is decoupled at *endo*-1*F*-azepine (**2b**). In general, we can apply such a potential energy surface manipulation strategy either by stabilizing **Endo-2** or destabilizing the N-inversion barrier for these coupled reactions. Interestingly, the stronger electron-withdrawing substitutions not only increase the **Endo-2** → **Exo-2** inversion barrier but also disfavors the transition state of direct **Endo-1** → **Exo-1** isomerization. In the case of -F substitution, the **1b** → **2b** → **3b** → **4b** pathway connects **1b** ⇌ **4b**. In contrast, **TS(1c → 4c)** connects **1c** ⇌ **4c** (**Endo-1** → **Exo-1**) with a significantly higher activation energy barrier ( $E_a = 17.1 \text{ kcal mol}^{-1}$ ). However, such isolobal

-CH<sub>3</sub> stereoelectronic induction accelerates the formation of *exo*-1*CH*<sub>3</sub>-azepine (**3c**) (see, Fig. 4(b)). In this case, **2c** → **3c** isomerization has such a small barrier which makes it a highly coupled pathway (**1c** → **3c**), a “dynamical” shift.<sup>48</sup>

In Fig. 4(a) and (b), snapshots of typical trajectories are shown. The reaction trajectories are simulated from these rate-limiting transition states, **TS(1b → 2b)** and **TS(1c → 2c)** respectively. In the case of -F substitution, a typical trajectory affords **2b** (**Endo-2**) within 109 fs and is stable in the simulation. However, the representative reaction trajectory forms **3c** (**Exo-2**) within 275 fs.

The 3D plots depict the typical trajectories simulated from rate-limiting TSs, **TS(1b → 2b)** and **TS(1c → 2c)** respectively



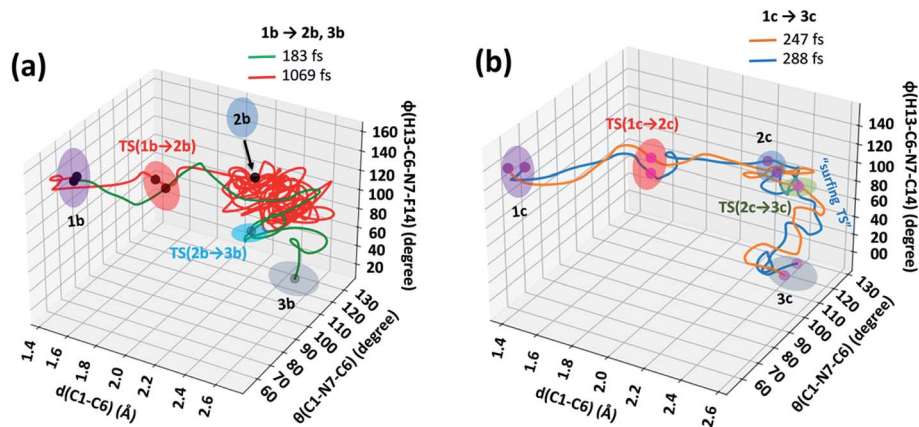


Fig. 5 3D-reaction plots for the valence isomerism reactions of (a)  $1b \rightarrow 2b, 3b$  and (b)  $1c \rightarrow 3c$ .

(see Fig. 5). In Fig. 5(a), two typical reaction trajectories are depicted. The red “normal” reaction trajectory elucidates the formation of **2b** *via* the steepest descent path (IRC-pathway), whereas the green flyby route shows the dynamical pathway (non-statistical) that can afford *exo*-product **3b** formation for the valence isomerism in **1b**. On the other hand, the orange and blue lines show fast conversion into the *N*-methyl substituted *exo*-1*H*-azepine (**3c**) (see Fig. 5(b)).

Further, we performed 156 reaction trajectory simulations from the **TS(1b  $\rightarrow$  2b)** at the M06-2X/6-31+G(d,p) level of theory (see ESI Fig. S4 and S5<sup>†</sup> for details). In this case, out of 132 (85%) product forming reaction trajectories, 87 (56%) afford *endo*-1*F*-azepine, **2b**. Interestingly, 45 (29%) reaction trajectories follow the dynamical (non-statistical pathways) routes to reach the *exo*-product (**3b**) zone. Therefore, the  $R = -F$  stereoelectronic modulation manipulates the stereoselectivity of the valence isomerism in **1b**. The stereoselectivity (**2b** : **3b**) of the reaction is 2 : 1.

In addition, a total of 145 reaction trajectories are propagated from the **TS(1c  $\rightarrow$  2c)** at the same level of theory (see ESI

Fig. S4 and S5<sup>†</sup> for details). Out of 141 (97%) productive trajectories, 104 (72%) follow the IRC path. Interestingly, out of 37 (25%) “corner cutting” reaction trajectories, 36 directly traverse through the *N*-CH<sub>3</sub> inversion **TS(2c  $\rightarrow$  3c)** and further dynamically fall out to the **3c**-zone, whereas only 1 “flyby” reaction trajectory leads to **2c**-product *via* **TS(2c  $\rightarrow$  3c)**. We found that *exo*-1-methyl-1*H*-azepine **3c** was the exclusive product (**Endo-2** : **Exo-2** = 1 : 140).

On the other hand, out of 104 “normal” reaction trajectories, 32 were dynamically stepwise. The 32 stepwise trajectories “surf” the **TS(2c  $\rightarrow$  3c)** dividing the surface before leaving the TS zone. The average surfing time at the **TS(2c  $\rightarrow$  3c)** zone is  $20.2 \pm 7.4$  fs (see the ESI, Fig. S5<sup>†</sup>). This is due to the conformational penalty which the methyl group needs to incur along the path **1c  $\rightarrow$  TS(2c  $\rightarrow$  3c)** while passing through the **TS(2c  $\rightarrow$  3c)** dividing the potential landscape. Quasielastic neutron scattering experiments are well-suited to recognize methyl-rotations in dynamically rich systems.<sup>53</sup>

Further, quantum mechanical tunneling (QMT) effects are investigated and they significantly dictate the benzene imine  $\rightleftharpoons$

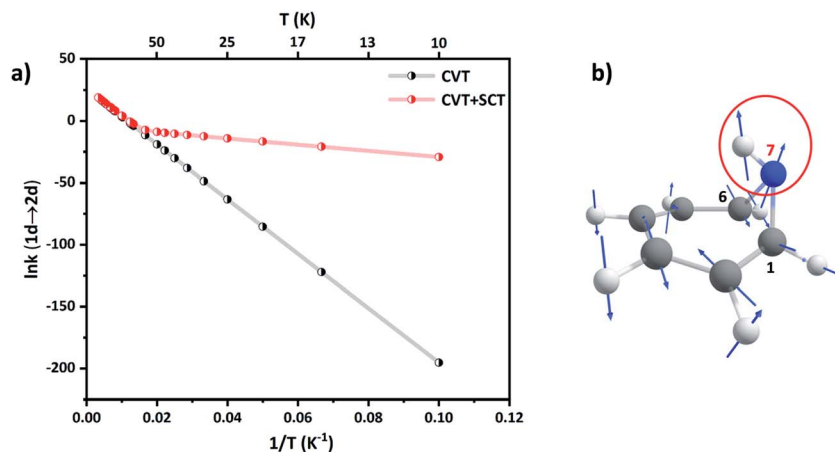


Fig. 6 (a) Arrhenius plot of the CVT and CVT + SCT rates (in  $s^{-1}$ ) for **1a  $\rightarrow$  2a**. (b) Displacement vectors for the normal mode of **TS(1a  $\rightarrow$  2a)**. The directional motion of the N7-H bond is encircled.



1H-azepine dynamics. Considering that  $\Delta G_{1 \rightarrow 2}^\ddagger$  (expansion) is the rate-limiting step along the preferred  $1 \rightarrow 2 \rightarrow 3$  pathway, ring isomerization of *endo*-benzene imine (**Endo-1**) to *endo*-1H-azepine (**Endo-2**) essentially would involve motion of the two bridged carbons (C1 and C6 in Scheme 2). A qualitative estimation of the width of the barrier ( $w$ ) is obtained by the difference in  $d(\text{C1-C6})$  between the benzene imine and azepine. For  $1\mathbf{a} \rightarrow 2\mathbf{a}$ ,  $w$  is only 0.75 Å which along with a small  $\Delta G_{1\mathbf{a} \rightarrow 2\mathbf{a}}^\ddagger = 4.4 \text{ kcal mol}^{-1}$  makes a strong case for heavy-atom tunneling.<sup>54,55</sup>

Since ring expansion is endergonic along  $1\mathbf{a} \rightarrow 2\mathbf{a}$ , the reaction rates are obtained by performing SCT dynamical calculations along the reverse (exergonic) direction followed by scaling them by microscopic reversibility.<sup>56</sup> At 300 K,  $k^{\text{CVT+SCT}}(1\mathbf{a} \rightarrow 2\mathbf{a}) = 1.84 \times 10^8 \text{ s}^{-1}$  while  $k^{\text{CVT}}(1\mathbf{a} \rightarrow 2\mathbf{a}) = 1.75 \times 10^8 \text{ s}^{-1}$ , acceleration by only 5% due to tunneling. However, at the liquid N<sub>2</sub> temperature,  $k^{\text{CVT+SCT}}(1\mathbf{a} \rightarrow 2\mathbf{a})$  and  $k^{\text{CVT}}(1\mathbf{a} \rightarrow 2\mathbf{a})$  are  $1.51 \times 10^{-1} \text{ s}^{-1}$  and  $3.64 \times 10^{-2} \text{ s}^{-1}$ , respectively, a gain of 75% by tunneling. The Arrhenius plot of the reaction rate shows strong curvature at low temperatures in Fig. 6(a). At 40 K,  $k^{\text{CVT+SCT}}(1\mathbf{a} \rightarrow 2\mathbf{a}) = 3.12 \times 10^{-5} \text{ s}^{-1}$  which is nine-orders more than the pure classical over-the-barrier transit. Such large enhancements in reaction rates at sub-cryogenic temperatures make ring-opening a highly QMT driven process.

Ring expansion along the C1–C6 bond also remotely affects the N–H bond at the bridgehead. The C1–N7–C6 bond angle increases from  $\theta(\text{C1-N7-C6}) = 63.9^\circ$  in  $1\mathbf{a}$  to  $\theta(\text{C1-N7-C6}) = 82.4^\circ$  in **TS**( $1\mathbf{a} \rightarrow 2\mathbf{a}$ ). Natural Bond Orbital (NBO)<sup>57</sup> calculations at the M06-2X/6-31+G(d,p) level (see the ESI, Table ST5†) show that the hybridization at the N-center changes from  $sp^2$  to  $sp^3$ . This should classically result in an inverse secondary KIE.<sup>58</sup> Indeed, secondary H/D isotope effects at CVT are inverse at all temperatures. For example,  $k^{\text{CVT}}(1\mathbf{a} \rightarrow 2\mathbf{a})/k^{\text{CVT}}(1\mathbf{d} \rightarrow 2\mathbf{d}) = 0.96, 0.89$  and  $0.32$  at  $T = 300 \text{ K}, 100 \text{ K}$  and  $10 \text{ K}$  respectively. However, the normal mode for ring-expansion also shows motion along the N–H(D) bond in the translation vector for the TS, see Fig. 6(b). Therefore, because the H-atom is lighter than D, tunneling assists  $1\mathbf{a} \rightarrow 2\mathbf{a}$  preferentially over  $1\mathbf{d} \rightarrow 2\mathbf{d}$ . This makes the secondary KIE positive at high temperatures and reduces the extent of inverse secondary KIE with  $k^{\text{CVT+SCT}}(1\mathbf{a} \rightarrow 2\mathbf{a})/k^{\text{CVT+SCT}}(1\mathbf{d} \rightarrow 2\mathbf{d}) = 1.08, 1.03,$  and  $0.42$  at  $T = 300 \text{ K}, 100 \text{ K},$  and  $10 \text{ K}$  respectively.

## Conclusion

Post-transition-state dynamics and quantum mechanical tunneling play an important role in the benzene imine  $\rightleftharpoons$  1H-azepine equilibrium. This isomerism belongs to a peculiar class of pericyclic reactions where ring expansion dictates stereoselectivity. The C–C bond cleavage and N-inversion dynamics guide the rich diversity of *endo*/*exo*-product outcomes. The dynamics can be selectively controlled by the electronic nature of the substituents on the N-end. While a strong electron-withdrawing group like –F decouples the ring-expansion and inversion pathways, for the –H/–CH<sub>3</sub> groups they are strongly entangled to result in the final ring-expanded form with N-inversion. At sub-cryogenic temperatures when the reaction is

driven by quantum mechanical tunneling, heavy-atom tunneling governs the reaction due to the small width of the barrier for ring expansion. Such coupled valence isomerism and N-inversion are also anticipated for other norcaradienes wherein the stereoelectronic effects of the substituents are critical.

## Data availability

The datasets supporting this article have been uploaded as part of the ESI.†

## Author contributions

NM performed the research, Ankita ran QMT calculations; CH did dynamics setup; AD planned the project.

## Conflicts of interest

The authors declare no competing financial interests.

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